DETAILED ACTION

1. This action is in response to papers field 4/09/2010.

2. The finality of the previous office action (12/10/2009) has been withdrawn based upon reconsideration of the claims and the art of record.

3. Claims 1-2 and 39-41 are pending. Claims 3-38 are cancelled.

4. The following rejections are newly applied.

5. This action is nonfinal.

Interview Summary

6. The reply filed on 4/09/2010 is a complete or accurate record of the substance of the phone interview of 3/15/2010.

Withdrawn Rejections

6. The 35 USC 103(a) rejections made in the previous office action (12/10/2009) are withdrawn after reconsideration of the claim language and the art. Specifically the art recited in the previous office action (12/10/2009) did not provide motivation for a microarray consisting of nucleic acid molecules that encode polypeptides of complex I, II, III, IV, or V being naturally coded for by a nuclear gene.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2 and 39-41 are rejected under 35 U.S.C. 112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 and 39-41 are indefinite. Claim 1 is drawn to a microarray "consisting of nucleic acid molecules". This phrase is indefinite because it requires the microarray to be limited to nucleic acid molecules without any solid support. It is not clear what structure would be encompassed by a microarray consisting only of nucleic acid molecules. It is suggested that the claim be amended to reflect that the nucleic acid set on the microarray consists of a particular genetic composition and not the microarray itself in order to encompass nucleic acids on a solid support.

With regard to Claim 2, the claim recites numerous nucleic acid molecules which are represented by a name and then a name within the parentheses. Parentheticals make the claim indefinite because it is unclear whether the information in the parentheses has the same, less, or more weight as the rest of the claim language. There are numerous polypeptides which are described as “ATP synthase” known in the art; however, the descriptor within the parentheses lists a particular type of ATP synthase. Therefore it is unclear if the applicant intends the claim to embrace all possible ATP synthase (as reflective of the language "ATP synthase"), or only a particular type of ATP synthase (as reflective of the language within the parentheses).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-2 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houstek et al. (Human Molecular Genetics 1999 Vol. 8 p 1967) in view of Chee et al. (WO 95/11995 May 4, 1995).

With regard to Claims 1-2, Houstek et al. teaches that mitochondrial ATPase (complex V) consists of 16 different polypeptides of which only 2 are products of mitochondrial genes whereas all other ATPase subunits are nuclear encoded (p. 1967 2nd paragraph). Houstek et al. teaches that although all mutations to date have been mtDNA mutations, that in the instant paper, a defect of ATPs was caused by altered

biosynthesis of the enzyme and has a nuclear origin (p. 1967 last paragraph to p. 1968 2nd paragraph). Houstek et al. teaches that this mutation is not an mtDNA defect and suggests screening the nuclear ATPase subunits to determine the location of the mutation (p. 1971 2nd full paragraph). Houstek et al. teaches that mtDNA encoded subunits assemble at a late stage (p. 1971 last paragraph) and therefore early stage defects could be caused by nuclear genes. Therefore Houstek et al. suggests that nuclear ATPase gene defects could be responsible for early stage defects. Houstek et al. suggests that nuclear ATPase subunits should be screened. Therefore Houstek et al. suggests a reason for the skilled artisan to use a composition consisting of nuclear genes.

However, Houstek et al. does not teach a microarray consisting of 90% nuclear encoded nucleic acid fragments from complex V. The art, at the time of filing, however, teaches that it is obvious to design microarrays to interrogate target sequences.

With regard to Claims 1-2, Chee et al teaches the design of an array comprising capture probes to make a block tiling array (see figure 16, p. 79 lines 23-39 and Figure 7, p. 37 lines 10-38). Chee et al. teaches the design of these tiling arrays to interrogate a reference sequence and its codons with a target sequence for the identification of single base mutants associated with disease (p. 11 lines 9-10 and p. 31 line 6-7). Chee et al. teaches that this design allows for simultaneous detection and quantification of multiple target sites (p. 32 lines 18-19). As such Chee et al. teaches a microarray which consists of a particular sequence that includes multiple probe sets that represent every permutation of the nucleotides for given sequence. Therefore Chee teaches a design

which will allow the analysis of all combinations of nucleotides surrounding a region of interest. As such the prior art teaches that once a region of interest is determined, in this case, the nuclear ATPase subunits, that a microarray comprising every permutation of that region can be designed for the purpose of identifying mutations associated with disease.

With regard to Claims 40-41, the array designed by Chee et al. would include every permutation of the target sequences of the nuclear ATP synthase of Houstek et al. and therefore would encompass at least 25 nucleic acid molecules.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to design a microarray consisting of nuclear ATP synthase genes using the design constraints of Chee et al. Houstek et al. suggest screening nuclear ATP synthase genes to determine the location of a defect caused in the early stage of development. The artisan thus would have been motivated to detect mutations within the nuclear ATP synthase genes that may affect function of the genes during development. Chee et al. teaches that the design of such microarrays to screen such mutations in simultaneous fashion was known in the art. As such the ordinary artisan would have a reasonable expectation of success of designing a microarray consisting of nucleic acid probes of the nuclear ATP synthase (complex V) genes for the expressed purpose of screening for early stage defects.

10. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Houstek et al. (Human Molecular Genetics 1999 Vol. 8 p 1967) and Chee et al. (WO 95/11995 May 4, 1995), as applied to 1-2 and 40-41 and in view of Hogan(US Patent 5541308 July 30, 1996).

Houstek et al. and Chee et al. suggest designing a microarray consisting of nucleic acid fragments of the nuclear genes of complex V (e.g. nuclear ATPase genes). However, Houstek et al. and Chee et al. do not teach probes of 40 nucleotides in length.

With regard to Claim 39, Chee et al. teaches that arrays can be designed such that a range of lengths of probes can be employed including probes of at least 30 nucleotides (p. 26 lines 23-25 and p. 27 lines 1-5).

Hogan et al. teaches that probes can be designed which detect target sequences such that the length is at least 40 nucleotides. Hogan et al. provides guidance for the selection of probes from a known region to detect a target. Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (see Column 10, lines 13-15). Therefore Hogan teaches design optimization to design probes that are at least 40 nucleotides in length.

Therefore it would be prima facie obvious to modify the microarray of Houstek and Chee et al. comprising nucleotide probes with the teaching of Hogan et al. to have probes of at least 50 nucleotides in length. Chee et al teaches that a range of lengths of probes can be employed (p. 26 lines 23-25). Therefore it would be considered routine optimization to include probes of at least 40 nucleotides in length. As Hogan teaches

that such lengths can be used in hybridization techniques, the length of the probes are known in the art to be used in detection methods. Therefore the ordinary artisan would have a predictable expectation of being able to design a microarray which encompasses probes of at least 40 nucleotides in length that can be used to detect the target.

11. Claims 1 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rustin et al. (Biochimica et Biophysica Acta Vol 1553 2002 p. 117) in view of Chee et al. (WO 95/11995 May 4, 1995).

With regard to claim 1, Rustin et al. teaches that complex II of mitochondrial respiratory chain cycle is composed of four subunits all of which are encoded by nuclear DNA (p. 117 1st paragraph). Rustin et al. teaches that defects within this region are relatively rare but are associated with a wide spectrum of clinical phenotypes ranging from encephalomyopahty in childhood to optic atrophy in adulthood (p. 118 1st column 2nd paragraph). Rustin et al. teaches that there are many mutations within complex II which cause various phenotypic defeats (p. 118 2nd column 2nd paragraph and the discussion of particular mutations on p. 118-119). As such Rustin et al. teaches that there are many mutations of the complex II genes which are associated with phenotypic defects. Rustin et al. teaches that complex II only comprise subunits which encompass polypeptides coded for by nuclear genes. Rustin et al. asserts that these nuclear genes of complex II could be involved in structural assembly defects (p. 121 last paragraph). Rustin et al. teaches mutations in complex II genes could be associated with newly

described diseases or of old disease of yet unknown mitochondrial origin (p. 121 last paragraph).

As such, Rustin suggests a use for the detection of mutations within the complex II region. Although Rustin et al. does not teach a microarray consisting of nuclear genes of complex II, the art at the time of filing teaches that it is obvious to place a known region on an array in order to detect mutational differences associated with diseases. Herein in the instant case, Rustin et al. suggests that complex II mutations can be involved with diseases and therefore the ordinary artisan would be motivated to detect mutations within complex II. As complex II only have nuclear genes, microarrays would consist of nuclear genes.

With regard to Claims 1-2, Chee et al teaches the design of an array comprising capture probes to make a block tiling array (see figure 16, p. 79 lines 23-39 and Figure 7, p. 37 lines 10-38). Chee et al. teaches the design of these tiling arrays to interrogate a reference sequence and its codons with a target sequence for the identification of single base mutants associated with disease (p. 11 lines 9-10 and p. 31 line 6-7). Chee et al. teaches that this design allows for simultaneous detection and quantification of multiple target sites (p. 32 lines 18-19). As such Chee et al. teaches a microarray which consists of a particular sequence that includes multiple probe sets that represent every permutation of the nucleotides for given sequence. Therefore Chee teaches a design which will allow the analysis of all combinations of nucleotides surrounding a region of interest. As such the prior art teaches that once a region of interest is determined, in this case, the nuclear ATPase subunits, that a microarray comprising every permutation

of that region can be designed for the purpose of identifying mutations associated with disease.

With regard to Claims 40-41, the array designed by Chee et al. would include every permutation of the target sequences of the nuclear ATP synthase of Houstek et al. and therefore would encompass at least 25 nucleic acid molecules.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to design a microarray consisting of complex II genes (e.g. consisting of nuclear genes) using the design constraints of Chee et al. Rustin et al. suggests that mutations within complex II genes can be associated with a number of phenotypic defects. The artisan thus would have been motivated to detect mutations within the complex II genes that may affect function of the genes during development. Chee et al. teaches that the design of such microarrays to screen such mutations in simultaneous fashion was known in the art. As such the ordinary artisan would have a reasonable expectation of success of designing a microarray consisting of nucleic acid probes of complex II for the expressed purpose of screening for diseases.

12. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rustin et al. (Biochimica et Biophysica Acta Vol 1553 2002 p. 117) and Chee et al. (WO 95/11995 May 4, 1995), as applied to 1-2 and 40-41 and in view of Hogan(US Patent 5541308 July 30, 1996).

Rustin et al. and Chee et al. suggest designing a microarray consisting of nucleic acid fragments of the nuclear genes of complex II (e.g. nuclear genes). However, Rustin et al. and Chee et al. do not teach probes of 40 nucleotides in length.

With regard to Claim 39, Chee et al. teaches that arrays can be designed such that a range of lengths of probes can be employed including probes of at least 30 nucleotides (p. 26 lines 23-25 and p. 27 lines 1-5).

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Therefore it would be prima facie obvious to modify the microarray of Rustin and Chee et al. comprising nucleotide probes with the teaching of Hogan et al. to have probes of at least 50 nucleotides in length. Chee et al teaches that a range of lengths of probes can be employed (p. 26 lines 23-25). Therefore it would be considered routine optimization to include probes of at least 40 nucleotides in length. As Hogan teaches that such lengths can be used in hybridization techniques, the length of the probes are known in the art to be used in detection methods. Therefore the ordinary artisan would have a predictable expectation of being able to design a microarray which encompasses probes of at least 40 nucleotides in length that can be used to detect the target.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Juliet C Switzer/
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